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Sleep characteristics in Goldenhar Syndrome

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ABSTRACT

Objective: To examine the characteristics of sleep in patients with Goldenhar Syndrome.
Design: Retrospective review of all polysomnography studies conducted at the University of North Carolina Hospitals between 2003 and 2013 on patients carrying the diagnosis of Goldenhar's Syndrome.
Results: A preponderance of patients demonstrated severe obstructive sleep apnea and hypercapnia.
Conclusions: Patients with Goldenhar Syndrome should be screened for sleep apnea and hypercapnia.

1. Introduction

Goldenhar Syndrome is a complex of aural, craniofacial, ocular and vertebral anomalies first distinguished from hemifacial microsomia in 1952. Although the aural anomalies are the most common, patients often manifest co-morbid cardiac, renal, and neurological abnormalities that are non-essential to diagnosis. A wide array of etiologies is thought to account for this presentation, and Hartsfield postulated a final common pathway of disturbance of the facial vasculature [1]. With an estimated prevalence of only 1/5600 live births [2], the combination of heterogeneity and rarity has impeded meaningful study and evidence-based management recommendations for these patients.

Logically, the anatomical cardinal features would predispose patients for sleep related airway disorders, particularly mandibular hypoplasia and glossoptosis [3]. Additionally those with neurological impairment may be at risk for hypoventilation or other issues of respiratory or sleep dysregulation. However, the relative paucity of studies examining nocturnal polysomnography leaves little empirical evidence to validate this position [4]. The only study to collect cardiorespiratory data did so without EEG, and pooled results across multiple craniofacial syndromes [5]. Summarily, sleep is minimally addressed in the existing literature, and solely as a subset of airway management. Even within this narrow field of inquiry, prognostic indicators are neither offered, nor constructed on the basis of published data. To address this gap, we present our case series to characterize sleep and its accompanying physiology in this population.

2. Methods and materials

This retrospective study was approved by the University of North Carolina (UNC) Institutional Review Board. A comprehensive database of sleep studies performed at the UNC Sleep Center was searched for all records pertaining to patients carrying the diagnosis of Goldenhar Syndrome between the years 2003–2013. Each diagnosis was confirmed by the Plastic Surgery service, Head and Neck Surgery service, or multi-disciplinary Craniofacial Center. All subjects underwent standard polysomnography including nasal pressure and measurement of CO_2 via transcutaneous or end tidal measures. In cases where more than one study was obtained, only the first diagnostic study was included. Therapeutic or repeat diagnostic studies were eliminated from the dataset. Data were extracted from the general medical record of each patient and their initial diagnostic sleep study. Sleep staging was based upon

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Table 1
Demographics.

Subject	Age	Sex	Race	Co-morbidities
A	5 yr 7 mo	M	Caucasian	None
B	3 wk	F	Caucasian	GERD
C	6 mo	M	Hispanic	None
D	1 yr 8 mo	M	Caucasian	Cleft palate, G-tube, hydrocephalus, static encephalopathy, rib deformity
E	7 yr 5 mo	M	Hispanic	Chronic otitis media
F	1 mo	M	Caucasian	None
G	2 yr 7 mo	F	African-American	Congenital brain anomaly, facial paresis
H	9 mo	F	Caucasian	Club foot, scoliosis, facial paresis, cervical rib, developmental delay, GERD, ventricular septal defect
I	5 yr 9 mo	F	Caucasian	None

GERD: gastro-esophageal reflux disease.

the Rechshaffen and Kales manual until 2007 and the AASM guidelines after 2007 [6]. To accommodate the change in scoring standard, Stages 3 and 4 of NREM sleep were combined into Stage N3. Respiratory events were scored as either apneas or hypopneas. Determination of obstructive, mixed or central origin was based on correlation to chest and abdominal movement. Apneas were defined as a ≥90% decreased airflow by nasal temperature lasting two breaths or longer. Central apneas were counted if an event was greater than 20 s or at least two breaths in duration and associated with an arousal or a 3% oxygen desaturation. Hypopneas were determined by a 50% or greater decrease in flow determined by nasal pressure lasting two breaths or longer and associated with an arousal or 3% oxygen desaturation. Respiratory event related arousals were not consistently measured across the study period. Hypoventilation was determined when end tidal CO_2 was greater than 50 torr for greater than 10% of the sleep period. Descriptive statistical analysis was performed on all data extracted.

3. Results

Nine individuals ranging from 3 weeks to 7 years 5 months in age were identified, 44% of them female. Median age for each gender was 20 months. Caucasians comprised two thirds of the series. Though relative to the general population in North Carolina African-Americans were relatively under-represented and Hispanics relatively over-represented, the ethnic distribution was roughly in line with national demographics. Concordant with this result, this disease does not have any reported racial predilection [2] (Table 1).

Mean sleep efficiency was 83.4% and mean sleep latency was 10.44 min. Data was highly variable, and standard deviation for all measured domains is consequently large. Nonetheless, mean progression through sleep staging was largely age-appropriate: 5.5% N1, 47.4% N2, 30% N3, and 17% REM (Table 2).

Respiratory data shows a preponderance of sleep apnea with AHI ranging from 0.3 to 43.74. No patient was able to sustain $SpO_2 > 93\%$ for the entirety of their study. Of the seven subjects for whom data was available, five were found to have elevated CO_2, either from sleep apnea or suggesting hypoventilation. Tracheostomy was required in 44% of subjects. All patients whose PSG results were ultimately supportive of the diagnosis of obstructive sleep apnea had symptoms suggestive of sleep issues such as noisy breathing or daytime behavioral symptoms which are clues to night time breathing issues (Table 3).

Table 2
Sleep architecture.

Subject	TST	Sleep latency	REM latency	Sleep efficiency	Stage N1 (%)	Stage N2 (%)	Stage N3 (%)	REM (%)
A	542	94	8	126.5	5.6	33.4	33.9	27.0
B	420.5	61	0	N/A		NREM 59.6		40.2
C	340	90	0	40	0	42.9	23.8	33.2
D	475	90	18	75	12.1	31.6	33.0	23.3
E	424.5	87	5.5		1.3	37.8	49.2	11.7
F	360.5	70	2	94	18.2	78.5	2.1	1.2
G	487	97	1.5	136	0.6	50.4	35.5	13.4
H	353.5	63	59	159	3.8	45	41.6	9.6
I	455	99	0	38.5	2.3	59.7	21.1	16.9

TST: total sleep time.
Sleep latency: time until the patient falls asleep.
REM latency: time until the patient enters Rapid Eye Movement sleep.
Sleep efficiency: percentage of total test time the patient was asleep.

Table 3
Respiratory data.

Subject	Ob AHI	Total AHI	RDI	Supine AHI	Highest CO_2	Lowest Sat	PLMI	Final Dx	Tracheostomy as Rx.
A	2.3	2.55	2.55	2.05	54	88	1.11	Mild sleep apnea and hypoventilation	N
B	43.5	43.7	43.7	43.74	NR	82	0	Severe OSA	Y
C	0.9	0.9	0.9	NR	45	91	3.71	Mild noisy breathing	N
D	1.97	1.97	1.97	NR	56	76	0	Sleep related hypoxemia, mild OSA	N
E	0	0.3	0.3	NR	51 (no REM)	92.9	7.6	Mild periodic limb mvmts	N
F	23.7	24.1	26.0	24.1	NR	82	0	Severe OSA	Y
G	0.38	0.5	2.1	0.7	47	90.9	6.5	Upper airway resistance	N
H	26.1	26.3	26.3	25.3	84	71.9	0	Severe OSA	Y
I	16.3	16.4	18.2	17.5	51	90.9	0.7	Severe OSA	Y

AHI: apnea-hypopnea index.
Ob AHI: obstructive AHI.
RDI: respiratory disturbance index.
PLMI: periodic limb movement index.

4. Discussion

We had a high preponderance of patients with sleep related breathing disorders in our series of patients with Goldenhar Syndrome. This retrospective series certainly is biased by individuals who were referred to the sleep laboratory but the overwhelming predominance of severe obstructive sleep apnea relative to milder forms of the disease deserves attention. This finding may reflect an intrinsic syndromic severity of the disease process in these patients, but upper airway obstruction in craniofacial disorders is often multi-level [4]. In the context of this syndrome, even putatively normal anatomic structures can contribute to airway obstruction through a variety of mechanisms. Individuals with neurological impairment may demonstrate dysfunction of the regulation of respiration only in sleep. Goldenhar patients with normal-sized tonsils have been reported to show evidence of obstruction [7]. The cumulative effect of these independent mechanisms may predispose to sleep apnea. However, the results Luna–Paredes group does not support this conclusion, reporting that 31% of patients pooled across several syndromes were negative for symptomatic screening, and only 15.9% of the total sample had severe obstructive sleep apnea [5]. Although pooled results, this incidence of severe obstructive sleep apnea is near-identical to the 16.9% reported for the general population [8]. Thus, it is unclear that the results apply to Goldenhar Syndrome. Second, their protocol defined failure to complete the questionnaire as a negative response, likely underestimating the incidence of symptomatology. Questions of severity notwithstanding, both studies suggest a relatively high incidence of obstructive sleep apnea in patients with Goldenhar Syndrome. Given this information, we recommend that clinicians maintain a high index of suspicion for obstructive sleep apnea in these patients.

Tracheostomy was undertaken twice as often in our study as in those previously generally reported by Sculerati but similar to the rate reported for specific entities such as Treacher Collins or Nager syndrome [4]. The difference may be partly attributable to the bias in subject selection, disease severity or differences in surgical management. Our review is unique in that clinic notes from our surgeons clearly document consideration and rationale for choosing tracheostomy over more conservative interventions based upon more severe multi-level airway obstruction characteristic of Goldenhar Syndrome, which necessitated the need for more aggressive intervention. It is possible this represents an evolution in understanding of the disease over the last 15 years. Our results also highlight the importance of OSA severity as a confounding variable distinct from Goldenhar's severity. More recent literature reveals the significant downstream effects of severe obstructive sleep apnea in children and the need for intervention [9]. Severe obstructive sleep apnea remains an indication for tracheostomy, and a recent retrospective review in an infant population demonstrates it had the greatest objective efficacy in reducing AHI of any medical or surgical intervention examined [10].

There was an unexpectedly high incidence of significant hypercapnia and hypoxia in the present study. Only two had a peak CO_2 recording below 50 torr, and none was able to maintain an O_2 saturation >93% for the entirety of the night. By contrast, an oxygen saturation of 92% represents the 5th percentile in normal children [11]. In other craniofacial disorders, it has been previously postulated but never demonstrated that syndromic central nervous system defects may increase their risk of respiratory abnormalities [12]. Neurological abnormalities have previously been reported in 17–50% of Goldenhar patients [12,13]. Three of the five of patients in this series with elevated end-tidal CO_2 had known neurophysiological abnormalities. Even excluding those patients with known brain lesions, the mean peak CO_2 value from the cases with available data was 50.25 torr. For many of these patients the elevation of CO_2 was separate from the periods of apnea and typically worse in REM sleep. These findings strongly suggest that some perturbation in the control of respiration exists and is intrinsic to the disease process; this finding strongly supports CO_2 monitoring during sleep as essential to determining sleep-related breathing issues in these patients.

Goldenhar Syndrome may have an increased prevalence and severity of obstructive sleep apnea and hypoventilation relative to the general population. Clinicians should maintain a high index of suspicion in screening for sleep disorders. Further research is needed to reassess the interplay between Goldenhar Syndrome and obstructive sleep apnea, given the tremendous strides made in our understanding of the latter disease since the mid-1990s. Additionally, a preponderance of our patients demonstrated significant episodes hypercapnia, and at least one episode of clinically significant hypoxia. These findings suggest overnight monitoring with capnography is an important adjunct for measuring respiratory derangement as a previously unrecognized aspect of sleep in this population. Future studies should aim to better characterize these events and their consequences. Increased awareness of and attentiveness to sleep-related pathophysiology in these patients will help to optimize their quality of life.

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